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(54) Fungicidal compositions

(57) Fungicidal compositions
displaying "resistance breaking" effects
and/or synergy, and having broader
spectra of activity, comprise a fungicide
(or co-fungitoxicant) which inhibits
adenosine deaminase or blocks sterol
biosynthesis in fungi and a further
fungicide having a different mode of
action.

GB 2 110 934 A

SPECIFICATION

Fungicidal compositions

5 This invention relates to compositions for combating plant fungi. More particularly the invention relates to mixtures of fungicidal substances containing a first fungicide which is either an inhibitor of adenosine deaminase or of sterol biosynthesis in fungi and at least one other anti-fungal substance having a different mode of anti-fungal effect.

10 It is known that plant fungi, especially races (strains, types) thereof, can develop resistance to, that is become insensitive to, anti-fungal chemicals thereby reducing the efficacy of a particular chemical. Indeed there are believed to be in existence certain plant fungal pathogens which are resistant to fungicides of the type which combat them, for example, by inhibiting their ability to biosynthesise

15 certain steroids essential to their metabolism, for example ergosterol. These fungicides, more specifically either block the incorporation of acetate into ergosterol an essential metabolic pathway of the fungus, thereby disrupting the synthesis and function of cell membranes by the fungus. Plant pathogens of the latter type include, in particular, races etc., of powdery mildew diseases such as *Erysiphe graminis* which infect cereal plants, for example crops of barley and wheat, and mildews

20 which infect non-cereal crops such as vines and apples, such latter diseases being, for example, *Uncinula necator*, *Podosphaera leucotricha* and *Sphaerotheca fuliginea* or other diseases such as *Venturia inaequatis* on apples or *Cercospora* leaf

25 spots on peanuts, banana and sugar beet.

It has now been found that certain mixtures of, or combinations of, fungicides are not only less prone than the individual components thereof to suffer from reduction in their efficacy due to resistant

30 (insensitive) species of plant pathogens infecting crops upon which they are sprayed (or the seed pre-treated with them), but in addition often display synergism, that is to say the combined antifungal effect of the mixture is greater than that which would

35 have been expected if the fungicidal components were acting separately. Such mixtures are ones in which a pyrimidine fungicide or a sterol biosynthesis inhibiting fungicide is combined with one or more fungicides having a different mode of action against

40 the fungal pathogens being combated.

45 According to the present invention there is provided an anti-fungal composition comprising either, as a first ingredient, a co-fungitoxicant or a fungicide which inhibits adenosine deaminase or a fungicide

55 having a sterol biosynthesis blocking mode of action in its anti-fungal effect, and at least one further fungicide having a different mode of action in combating fungi.

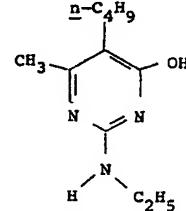
The fungicide which inhibits adenosine deaminase

60 in fungi may be a pyrimidine fungicide and by "a pyrimidine fungicide" is intended single ring compounds such as ethirimol, dimethirimol and bupirimate. The term is not intended to embrace bicyclic and tricyclic compounds in which a central carbon

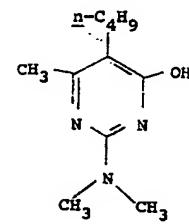
65 atom bears a pyrimidine ring and one or more other aryl or heterocyclic rings.

The co-fungitoxicant need have no fungicidal activity in its own right; or have activity only against triazole resistant strains of a pathogen.

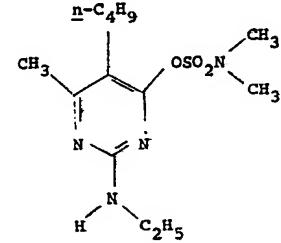
70 The fungicidal ethirimol is the subject of British Patent No. 1182584 and it has the chemical structure:-



The fungicide dimethirimol is also the subject of British Patent No. 1182584 and it has the chemical structure:-



The fungicide bupirimate is the subject of British Patent No. 1400710 and it has the chemical structure:-



80 The foregoing fungicides are, as already stated, considered to have an anti-fungal effect by inhibition of the action of adenosine deaminase in the meta-

Certain of the /The Chemical/mathematical formula(e) appearing in the printed specification was/were submitted after the date of filing, the formula(e) originally submitted being incapable of being satisfactorily reproduced.

The matter shown in the printed specification between square brackets was furnished after the filing date of the application, the application as filed being defective as regards this matter.

This print embodies corrections made under Section 117(1) of the Patents Act 1977.

This print takes account of replacement documents later filed to enable the application to comply with the formal requirements of the Patents Rules 1982.

bolism of fungi.

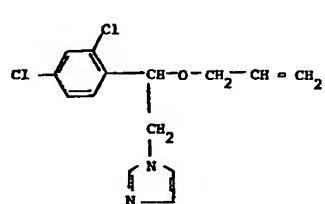
In a further aspect, therefore, the invention provides an anti-fungal composition comprising a fungicide which is ethirimol, dimethirimol or bupirimate 5 or an anti-fungal substance which is an inhibitor of the ability of the fungus to biosynthesise sterols and

at least one further fungicide which has a different mode of action in combating fungi. Examples of fungicidal substances having the capacity to inhibit 10 sterol biosynthesis and the classes to which the belong, are as follows:—

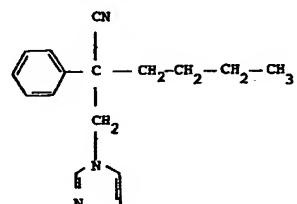
| CLASS AND COMMON NAME OF FUNGICIDE | TRADE NAMES OF FUNGICIDAL PRODUCTS CONTAINING THE FUNGICIDE |
|--|---|
| <i>Imidazoles</i> | |
| Imazalil | Fungaflor, present in Mist-O-Matic Murbanine Plus, Mist-O-Matic Muridal Seed Treatment Sportak |
| Prochloraz | — |
| Fenaponil | — |
| <i>Piperazines</i> | |
| Triforine | Saprol, Triforine LST, present in Nimrod T |
| <i>Pyridines</i> | |
| Buthiobate | Paron |
| EL 241 | — |
| <i>Piperidines</i> | |
| Fenpropidin | — |
| <i>Pyrimidines</i> | |
| Fenarimol | Rubigan |
| Nuarimol | Triminol, present in Mist-O-Matic Murox Seed Treatment |
| Triarimol | — |
| <i>Triazoles</i> | |
| Bitertanol | — |
| Diclobutrazol | Vigil, present in Vigil K, present in Vigil T Persulon |
| Fluotrimazole | Tilt 250 EC, in Tilt mbc 45WP |
| Propiconazole | Bayleton, Bayleton 5, in Bayleton, BM, Bayleton CF |
| Triadimefon | Baytan Vanguard, Sonax |
| Triadimenol | — |
| Etaconazole | — |
| PP969 | — |
| <i>Morpholines</i> | |
| Dodemorph | BASF F238 |
| Fenpropimorph | Corbel, Mistral |
| Tridemorph | Calixin, Bardew, Beacon, Cosmic |

The chemical structures of the foregoing chemical substances are set out below:—

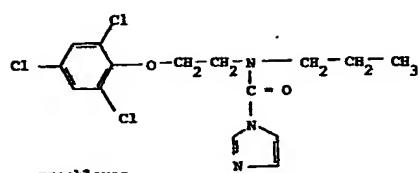
IMIDAZOLES



imazalil

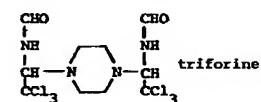


fenaponil



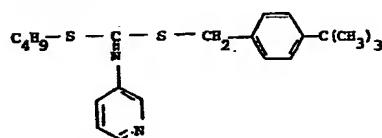
3rochloraz

PIPERAZINES

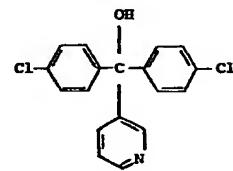


orine

PYRIDINES

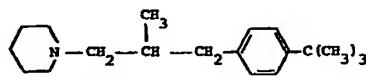


buthiobate



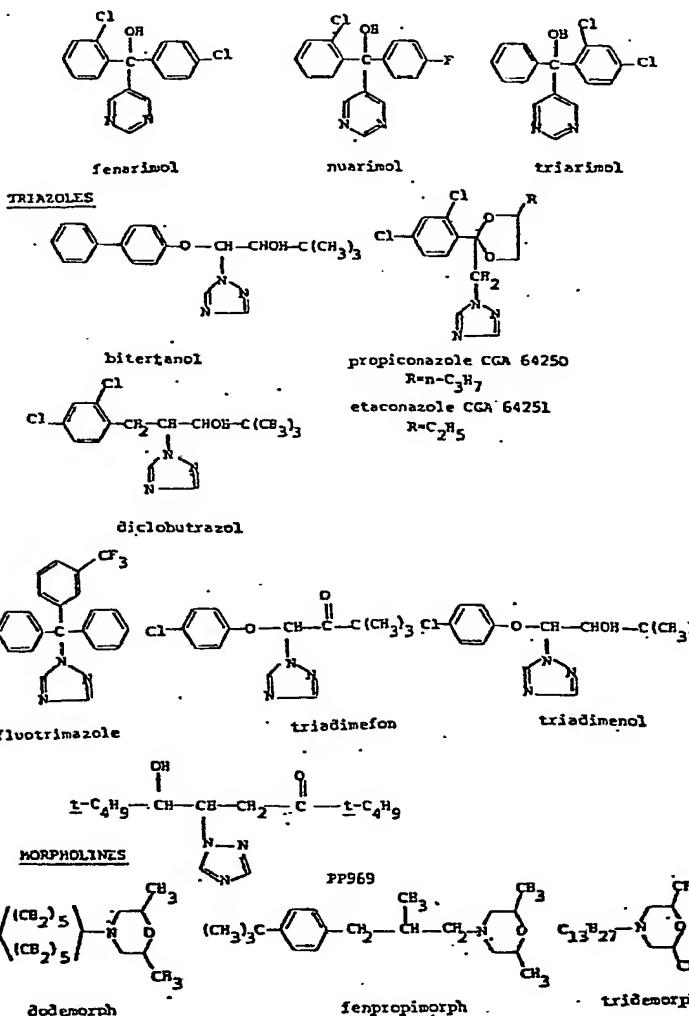
EL-241

PIPERIDINES



fenpropidin

PIRAMIDES



In a further aspect, therefore, the invention provides a fungicidal composition comprising, as active ingredients, a first fungicide which is either ethirimol, dimethirimol or bupirimate or which is an

5 inhibitor of the ability of a plant fungus to biosynthesise sterols and is a specific fungicidal substance
from the foregoing list of chemical compounds, and
at least one further fungicidal substance having a
mode of action in combating fungi which is different
10 from that of the first fungicide.

As far as suitable further fungicidal substances are concerned these may be any general, i.e. metabolic, inhibitor of plant fungal growth, for example a respiratory inhibitor.

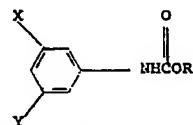
15 By the term "general metabolic inhibiting agent" (including respiratory inhibitors) are intended fungicidal and anti-fungal substances such as those listed below under chemical class headings with examples of specific fungicides listed and an indication of their
20 believed mode of action.

Table B

| | |
|--|--|
| 1. Site specific inhibitors | |
| <i>Acylalanies</i> | –furalaxyl, metalaxyl, ofurace, galben. |
| <i>Mode of action</i> | –? |
| <i>Antibiotics</i> | –cycloheximide etc. |
| <i>Mode of action</i> | –inhibits protein synthesis |
| <i>Benzimidazoles</i> | –benomyl, carbendazim, thiophanate methyl, thiabendazole, fuberidazole |
| <i>Mode of action</i> | –inhibition of mitosis |
| <i>Carboxamides</i> | –carboxin, oxycarboxin, methfuroxam, fenfuram, furmecyclo, benodanil, pyracarbolid |
| <i>Mode of action</i> | –interference with respiration by blocking succinate dehydrogenase |
| <i>Dicarboxamides</i> | –iprodione, procymidone, vinclozolin, M8164 (Serinal) |
| <i>Mode of action</i> | –interference with mitotic segregation |
| <i>Aromatic hydrocarbons</i> | –2-phenylphenol, sodium -o-phenyl-phenate biphenyl, chloraneb, dichloran, quintozene, tecnazene. |
| <i>Mode of action</i> | –interference with mitotic segregation |
| <i>Dinitrophenols</i> | –dinapacryl, dinocap |
| <i>Mode of action</i> | –uncouplers of oxidative phosphorylation |
| <i>Dimethyldithiocarbamates</i> | –thiram |
| <i>Mode of action</i> | –inhibitors of pyruvate dehydrogenation |
| <i>Guanidines</i> | –dodine, guazatine |
| <i>Mode of action</i> | –affect cell membrane permeability |
| <i>Organotin compounds</i> | –fentin |
| <i>Mode of action</i> | –inhibition of oxidative phosphorylation |
| <i>Organic phosphates and isoprothiolane</i> | –pyrazophos, edifenphos, BP, –isoprothiolane |
| <i>Mode of action</i> | –inhibition of the conversion of phosphatidyl-ethanolamine to phosphatidyl-choline |
| <i>Acetamides</i> | –curzate |
| <i>Mode of action</i> | –unknown |
| <i>Aminobutane</i> | –2-aminobutane |
| <i>Mode of action</i> | –inhibition of pyruvic dehydrogenase |
| <i>Anthraquinones</i> | –dithianon |
| <i>Mode of action</i> | –inhibition of glycolysis |
| <i>Isoxazolones</i> | –drazoxalon |
| <i>Mode of action</i> | –uncoupler of respiration |
| <i>Nitroisophthalates</i> | –nitrothal-isopropyl |
| <i>Mode of action</i> | –unknown |
| <i>Organic phosphates</i> | –ditalimfos |
| <i>Mode of action</i> | –disrupts metabolism |
| <i>Quinoxalines</i> | –quinomethionate |
| <i>Mode of action</i> | –? |
| <i>Sulphamides</i> | –dichlofluanid, tolyfluanid |
| <i>Mode of action</i> | –? |
| <i>Thiocarbamates</i> | –prothiocarb, propanocarb |
| <i>Mode of action</i> | –causes cell membrane dysfunction |

N-Phenylcarbamate derivatives

Such as those disclosed in European Patent Application No. 81109561.1 (Publication No. 51871) having the general formula:



5 where X and Y are alkyl, alkoxy or halogen and R is methol or ethyl.

Table C

| | |
|--------------------------------|---|
| <i>Thiadiazoles</i> | -etridazole |
| Mode of action | -interferes with respiration |
| 2. Multisite inhibitors | |
| <i>Dithiocarbamates</i> | -maneb, zineb, mancozeb, nabam, propineb etc. |
| Mode of action | -inhibitors of thiol groups |
| <i>Phthalimides</i> | -captafol, captan, folpet |
| Mode of action | -inhibitors of thiol groups |
| <i>Phthalonitriles</i> | -chlorothanlonil |
| Mode of action | -inhibitor of thiol groups |
| <i>Copper compounds</i> | -various |
| Mode of action | -? |
| <i>Mercury compounds</i> | -various |
| Mode of action | -? |
| <i>Sulphur</i> | - |
| Mode of action | -? |
| <i>Aluminium compounds</i> | -FOSETYL ALUMINIUM |
| Mode of action | -? |

Anionic agents

| |
|---|
| Sodium dodecylbenzene sulphonate |
| Sodium dodecylsulphate |
| Sodium C13/C15 alcohol ether sulphonate |
| Sodium ceto stearyl phosphate ester |
| Diocetyl sodium sulphosuccinate |
| Sodium isopropyl naphthalene sulphonate |
| Sodium methylene bis naphthalene sulphonate |

Cationic agents

| |
|--|
| Cetyl trimethyl ammonium chloride |
| Salts of long chain primary, secondary or tertiary amine |
| Alkyl propylene amines |
| Lauryl pyridinium bromide |
| Quaternised fatty amine ethoxylate |
| Alkyldimethyl benzyl ammonium chloride |
| 1 - Hydroxyethyl - 2 - alkyl imidazoline. |

In a further aspect, therefore, the invention provides a fungicidal composition comprising, as active ingredients, a first fungicide which is either ethirimol, dimethirimol or bupirimate or which is an inhibitor of the ability of a plant fungus to biosynthesise sterols and is a specific fungicidal substance from the foregoing list of chemical compounds, and at least one further fungicidal substance having a mode of action in combating fungi which is different from that of the first fungicide and which is a substance chosen from the specific fungicidal subst-

ances recited in the immediately preceding list.

The invention also provides a process for treating 20 seed which comprises dressing seed with a composition according to the invention.

In another aspect seed may be dressed first with ethirimol, or with a fungicide which inhibits sterol biosynthesis in plant fungi and then with a further 25 fungicide as defined above. Batches of seed treated separately with a first fungicide and with a further fungicidal substance may be mixed with untreated seed, e.g. tumbled therewith, so as to produce a

batch of treated seed.

The invention further provides, in yet another aspect, a process for combating plant fungi which comprises applying to a plant, to seed of a plant, or 5 to the locus of a plant or seed, an anti-fungal composition as defined in any of the preceding paragraphs.

In a still further aspect the invention provides a process of combating plant fungi which comprises 10 alternately treating, e.g. spraying, crops with ethirimol, dimethirimol or bupirimate, or with a fungicide which inhibits sterol biosynthesis in plant fungi, and then with a further fungicidal substance as defined above.

15 The amounts of fungicidal substance used in the invention compositions can readily be determined by simple experimentation, but in general, in view of the ability to counter resistant (insensitive) races etc., of fungi and/or the synergism displayed, it is not 20 necessary to use the full rates of chemical normally applied.

EXAMPLE 1

A series of initial experiments were carried out to determine the efficacy of a range of co-fungitox-25 icants in controlling two isolates of *E. graminis* f.sp *hordei* in the absence of triadimefon with the following results (Table 1).

Sumiscrex showed activity against one or both fungus isolates whereas Sanspor and Terrazole 30 were inactive.

Sumiscrex was further tested to determine in more detail its rate response against the two isolates of *E. graminis* f.sp *hordei* (Table 2). Based on these data, suboptimal rates of this compound were chosen for 35 a further interaction experiment involving triadimefon (Tables 3 and 4).

Against both isolates the addition of Sumiscrex at 150 ppm to triadimefon at 0.1 ppm boosted the activity of triadimefon in the degree of disease 40 control achieved. The margin of this increase in activity must be accounted for by a synergistic interaction between the two compounds.

Materials and Methods

1. *Plant Sowing*: Approximately 10 seeds/pot of 45 Golden Promise spring barley were sown into John Innes compost number one in minipots.

1.1 *Growth Conditions*: Day temperature 21°C, Relative Humidity 60%, Night temperature 17°C, Relative Humidity 95%, 16 hours daylength. The plants 50 were watered by an automatic watering system.

2. *Test Method for spraying the plants*: Plants were sprayed at 6 days old; the chemicals under test were made up in 0.03% Tween 20; and the plants were sprayed to give an even coverage on both leaf 55 surfaces, using a hand-held De Vilbiss spray gun at 15 psi (pounds per square inch).

After spraying, the plants were transferred to a second growth chamber for 24 hours to allow plants to dry.

60 2.1 *Growth Conditions in this room were*: Day temperature 24°C, Relative Humidity 60%, Night temperature 17°C, Relative Humidity 95%, 16 hours daylength. The plants were watered by an automatic watering system.

65 3. *Method for preparing the repli dishes*: Plants

were removed from the Growth Room and cut into 2 cm lengths from just below the tip of the prophyll. Only uniform plants were chosen. Only one leaf piece was taken from each prophyll. The cut leaf

70 pieces were then placed into a slit in the agar in the repli dish. (the dishes contained 45 ml of 10% Tap water agar), the top rate of chemical first proceeded by lower rate. For each chemical rate there were 5 replicate leaf pieces.

75 When changing from one rate of chemical to a lower rate the scissors and forceps were wiped with a swab soaked in Methanol to avoid contamination. Particular attention was paid to ensure that the leaf pieces did not touch the lid nor overlap one another 80 in the dish. The former would cause condensation to run down the leaf pieces and could wash off some spores, the latter would lead to uneven inoculation and hence misleading results.

4. *Inoculation Method*: Infected leaf pieces were 85 cut from stock plants in propagating tubes and placed in petri dishes on moist foam squares 48 hours prior to inoculation. The infected leaf pieces were kept in a 19°C constant temperature room with a 16 hour day length.

90 Repli dishes were inoculated using a settling tower, the tower was placed over the opened repli dish and sporulating leaf pieces held in forceps were placed in the nose of the tower. An air line set at 3/4 lb per square inch pressure was used to blow the 95 spores off the leaf pieces and into the settling tower.

The repli dishes remained inside the tower for 2 minutes after which the tower was removed and the lid replaced on the repli dish. The tower, forceps and air lines were swabbed with Methanol to decom-100 taminant them.

Once all the repli dishes were inoculated they were placed in a 19°C constant temperature room with a 16 hour daylength where they remained until assessment 6 days later.

105 5. *Assessment*: Percentage sporulating disease was assessed on each leaf piece.

TABLE 1
Disease Control
Erysiphe graminis f.sp *hordei*
isolate

| Fungitoxicant | Rate ppm ai. | 1 | 2 |
|----------------------------|-----------------|----|-----|
| Sumisplex (procymidone) | 500 | 99 | 100 |
| | 250 | 98 | 100 |
| | 125 | 65 | 39 |
| | 100 | 93 | 56 |
| | 50 | 98 | 25 |
| | 0 | 0 | 0 |

TABLE 2
2 % Disease Control
Erysiphe graminis f.sp *hordei*
isolate

| Fungitoxicant | Rate ppm ai. | 1 | 2 |
|----------------------------|-----------------|----|----|
| Sumisplex (procymidone) | 250 | 99 | 87 |
| | 200 | 96 | 30 |
| | 175 | 97 | 69 |
| | 150 | 27 | 57 |
| | 125 | 22 | 27 |
| | 0 | 0 | 0 |

TABLE 3
Isolate 1 % Disease Control

| | Triadimefon | Triadimefon |
|-------------------------------|-------------------|-------------|
| Rate | | + |
| ppm ai | 150 ppm Sumisplex | |
| 0.25 | — | |
| 0.1 | 59 (20) | |
| 0.05 | 30 | |
| 0.025 | 43 | |
| 0.01 | — | |
| Sumisplex | 150 | 0 |
| Untreated | — | 0 |
| Actual | 74% | |
| untreated disease level | | |

() = Activity of triadimefon alone in same test dish
at 0.1 ppm.

TABLE 4
Isolate 2 % Disease Control

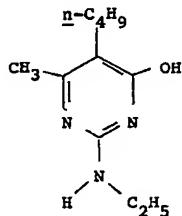
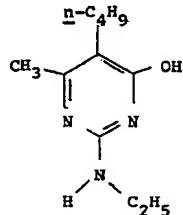
| | Triadimefon | Triadimefon |
|---------------|-------------------|-------------|
| Rate | | + |
| ppm ai | 150 ppm Sumisplex | |
| 0.5 | 93 (52) | |
| 0.25 | 0 | |
| 0.1 | —15 | |
| 0.05 | | |
| Sumisplex | 150 | —31 |
| Untreated | — | 0 |
| Actual | | |
| Untreated | | 61% |
| Disease level | | |

() = Activity of triadimefon in same test dish at
0.1 ppm.

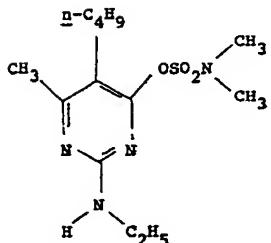
CLAIMS

1. An anti-fungal composition comprising as a first ingredient either a co-fungitoxicant or a fungicide which inhibits adenosine deaminase or a fungicide having a sterol biosynthesis blocking mode of action in its anti-fungal effect, and at least one further fungicide having a different mode of action in combating fungi.

2. An anti-fungal composition according to claim 10 1 comprising a adenosine deaminase inhibitor which is a pyrimidine derivative having the structure:



or



3. An anti-fungal composition according to claim 1 comprising a fungicide having a sterol biosynthesis blocking mode of action and which is an imidazole, piperazine, pyridine, piperidine, pyrimidine, triazole or morpholine derivative as hereinbefore defined.

4. An anti-fungal composition according to any 20 of the preceding claims wherein the further fungicide is a site specific inhibitor or multisite inhibitor, as hereinbefore defined, or a general, eg. metabolic, inhibitor of fungal growth.

5. An anti-fungal composition according to any 25 of the preceding claims wherein the further fungicide comprises any of the specific fungicidal substances defined hereinbefore.

6. A process for treating seed which comprises dressing seed with a composition according to the 30 invention.

7. A process for dressing seed wherein seed is dressed first with ethirimol, or with a fungicide which inhibits sterol biosynthesis in plant fungi, and then with a further fungicide as defined in any of the

35 preceding claims.

8. A process for combating plant fungi which comprises applying to a plant, to seed of a plant, or to the locus of a plant or seed, an anti-fungal composition as defined in any of the proceeding 40 claims.

9. A process of combating plant fungi which comprises alternately treating, eg. spraying, crops with ethirimol, dimethirimol or bupirimate, or with a fungicide which inhibits sterol biosynthesis in plant 45 fungi, and then with a further fungicidal substance as defined above.

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